STN Search History

FILE 'HOME' ENTERED AT 15:42:24 ON 01 JUN 2004

L1 112 (PAPILLOMA! OR POLYOMA!) (P) (ADJUVANT OR CPG OR (OLIGONUCLEOTID
E OR POLYNULCEOTIDE OR NUCLEIC) (3N) (IMMUNOMOD! OR IMMUNOSTIM!)
)

L4 4 L3 AND (CPG OR (OLIGONUCLEOTIDE OR POLYNULCEOTIDE OR NUCLEIC))

L5 1365 (INTERFERON (A) ALPHA OR INTERFERON-ALPHA) (P) (ADJUVANT OR CPG
OR (OLIGONUCLEOTIDE OR POLYNULCEOTIDE OR NUCLEIC) (3N) (IMMUNOMO
D! OR IMMUNOSTIM!))

L9 316 (IFN-ALPHA OR IFN (A) ALPHA OR INTERFERON (A) ALPHA OR INTERFERO
N-ALPHA) (S) (CPG OR (OLIGONUCLEOTIDE OR POLYNULCEOTIDE OR NUCLE
IC) (3N) (IMMUNOMOD! OR IMMUNOSTIM!))

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(FILE 'HOME' ENTERED AT 15:42:24 ON 01 JUN 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 15:42:46 ON
01 JUN 2004

L1 112 S (PAPILLOMA! OR POLYOMA!) (P) (ADJUVANT OR CPG OR (OLIGONUCLEO
L2 35 DUP REM L1 (77 DUPLICATES REMOVED)
L3 30 S L2 NOT PY>2001
L4 4 S L3 AND (CPG OR (OLIGONUCLEOTIDE OR POLYNULCEOTIDE OR NUCLEI
L5 1365 S (INTERFERON (A) ALPHA OR INTERFERON-ALPHA) (P) (ADJUVANT OR C
L6 13 S L1 AND L5
L7 4 DUP REM L6 (9 DUPLICATES REMOVED)
L8 4 S L7 NOT L4
L9 316 S (IFN-ALPHA OR IFN (A) ALPHA OR INTERFERON (A) ALPHA OR INTERF
L10 316 S L9 NOT L6
L11 106 S L10 NOT PY>2001
L12 40 DUP REM L11 (66 DUPLICATES REMOVED)
L13 0 S L12 AND (PAPILLOM! OR POLYOMA!)
L14 0 S L12 AND (PAPILLOMAVIR######)

L8 ANSWER 2 OF 4 MEDLINE on STN
AN 2001072914 MEDLINE
DN PubMed ID: 10923940
TI Current advances in the basic research and clinical management of juvenile-onset recurrent respiratory papillomatosis.
AU Bergler W F; Gotte K
CS Department of Otolaryngology, Head and Neck Surgery, University Hospital Mannheim, Germany.. wolfgang.bergler@hno.ma.uni-heidelberg.de
SO European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery, (2000) 257 (5) 263-9. Ref: 80
Journal code: 9002937. ISSN: 0937-4477.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010103
AB Juvenile-onset recurrent respiratory papillomatosis is a relatively uncommon disease that presents clinically with symptoms ranging from hoarseness to severe dyspnea. Human papilloma viruses type 6 and 11 are important in the etiology of the papillomata and are most probably transmitted from mother to child during childbirth. Although spontaneous remission is frequent, a rare fatal course because of pulmonary spread or malignant transformation has occurred. CO2 laser evaporation of **papillomas** and **adjuvant** drug therapy using lymphoblastoid **alpha-interferon** are the most common treatment modalities at present. However, several other treatment modalities have been tried with varying success. Recent advances in basic research and different therapeutic approaches are reviewed.

L8 ANSWER 3 OF 4 MEDLINE on STN
AN 94169061 MEDLINE
DN PubMed ID: 8123576
TI Buschke-Loewenstein tumour infiltrating pelvic organs.
AU Grassegger A; Hopfl R; Hussl H; Wicke K; Fritsch P
CS Department of Dermatology, University of Innsbruck, Austria.
SO British journal of dermatology, (1994 Feb) 130 (2) 221-5.
Journal code: 0004041. ISSN: 0007-0963.
CY ENGLAND: United Kingdom
DT (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199404
ED Entered STN: 19940420
Last Updated on STN: 19940420
Entered Medline: 19940414
AB We report a 42-year-old HIV-negative patient with a 12-year history of exceptionally extensive genital warts and coexisting verrucous carcinoma of the anogenital region (Buschke-Loewenstein tumour). Masses of both tumour and viral **papillomas** infiltrated the external genitalia, perineum and buttocks, pelvic diaphragm and parts of the lesser pelvis, as well as the urethra, prostate and parts of the urinary bladder, necessitating repeated surgical intervention and plastic reconstruction.

Adjuvant interferon-alpha therapy was given
without any lasting effects. Human papillomavirus type 6 was detected by DNA in situ hybridization and Southern blot analysis.

L12 ANSWER 3 OF 40 MEDLINE on STN DUPLICATE 3
AN 2001697965 MEDLINE
DN PubMed ID: 11745372
TI Distinct **CpG** oligonucleotide sequences activate human gamma delta T cells via **interferon-alpha**/-beta.
AU Rothenfusser S; Hornung V; Krug A; Towarowski A; Krieg A M; Endres S; Hartmann G
CS Department of Internal Medicine, Division of Clinical Pharmacology, University of Munich, Munich, Germany.
SO European journal of immunology, (2001 Dec) 31 (12) 3525-34. Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200201
ED Entered STN: 20011218
Last Updated on STN: 20020128
Entered Medline: 20020124
AB Oligodeoxynucleotides with CpG motifs (CpG ODN) mimic microbial DNA and activate effectors of innate immunity including NK cells. Human gamma delta T cells (Vgamma9/Vdelta2) are antigen specific "natural memory" T cells in a preactivated stage, which respond to common non-protein phosphoantigens. Among several **CpG** ODN tested, distinct **CpG** ODN sequences characterized by inducing high amounts of **IFN-alpha**/-beta in PBMC elicited strong gamma delta T cell and NK cell responses, as determined by CD69 expression, IFN-gamma production, perforin content and lytic activity. These CpG ODN activated gamma delta T cells and NK cells in the absence of an additional stimulus and synergistically increased responsiveness to cell-type-specific antigens like isopentenylpyrophosphate for gamma delta T cells and NK-sensitive tumor cells for NK cells. NK cells and gamma delta T cells were activated via **IFN-alpha**/-beta released by **CpG** ODN-stimulated PBMC. Purified gamma delta T cells and NK cells did not respond to **CpG** ODN but to recombinant **IFN -alpha**/-beta. In conclusion, **CpG** ODN sequences were identified which, based on their ability to induce high amounts of **IFN-alpha**/-beta, represent strong adjuvants for "natural memory" cells including responses of gamma delta T cells to non-protein antigens. Early **IFN-alpha**/-beta dependent stimulation of IFN-gamma synthesis in NK cells and gamma delta T cells may contribute to the **CpG** ODN-induced Th1 bias of an evolving immune response.

L12 ANSWER 7 OF 40 MEDLINE on STN DUPLICATE 6
AN 2001397419 MEDLINE
DN PubMed ID: 11449369
TI Identification of **CpG** oligonucleotide sequences with high induction of **IFN-alpha**/beta in plasmacytoid dendritic cells.
AU Krug A; Rothenfusser S; Hornung V; Jahrsdorfer B; Blackwell S; Ballas Z K; Endres S; Krieg A M; Hartmann G
CS Department of Internal Medicine, Division of Clinical Pharmacology, University of Munich, Munich, Germany.
NC CA66570 (NCI)
DK25295 (NIDDK)
DK54759 (NIDDK)
SO European journal of immunology, (2001 Jul) 31 (7) 2154-63. Journal code: 1273201. ISSN: 0014-2980.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010906
Entered Medline: 20010809
AB The immature plasmacytoid dendritic cell (PDC) is identical with the principal type I IFN-producing cell upon viral infection. Oligodeoxynucleotides which contain unmethylated CpG motifs (CpG ODN) are recognized by the vertebrate immune system. Previously, we described CpG ODN that strongly activate human B cells and human blood dendritic cells. Here we describe distinct **CpG**-containing oligonucleotide sequences which, in contrast to previously described **CpG** ODN, induced high amounts of **IFN-alpha** and IFN-beta in peripheral blood mononuclear cells (PBMC). Intracellular staining for **IFN-alpha** revealed that within PBMC **CpG** ODN-induced **IFN-alpha** is produced exclusively by PDC. Unlike **IFN-alpha**, TNF-alpha is up-regulated in PDC by all **CpG** ODN tested. Purified PDC responded to CpG ODN, demonstrating direct activation of PDC by CpG ODN. The most active sequence induced the production of up to 5 pg IFN-alpha per single PDC, resulting in more than 400 ng/ml IFN-alpha in the supernatant of PBMC enriched for PDC. The potency of **CpG** ODN to stimulate **IFN-alpha** correlated with their ability to stimulate NK cell lytic activity, while purified NK cells did not respond to **CpG** ODN. IFNgamma production in PBMC was dependent on **CpG** ODN-induced **IFN-alpha**/beta as demonstrated by **IFN-alpha**/beta blocking antibodies. **IFN-alpha**-inducing **CpG** ODN strongly supported IFN-gamma production of TCR-triggered CD4 T cells but were less active than other **CpG** ODN in stimulating B cells. In conclusion our results demonstrate that particular **CpG** ODN sequences exist which, due to high **IFN-alpha**/beta induction in PDC, induce a set of immune responses typical for viral infection.

L12 ANSWER 11 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
AN 2001:523351 CAPLUS
DN 136:165878
TI CpG-DNA derived from sera in systemic lupus erythematosus enhances ICAM-1 expression on endothelial cells
AU Miyata, M.; Ito, O.; Kobayashi, H.; Sasajima, T.; Ohira, H.; Suzuki, S.; Kasukawa, R.
CS Department of Internal Medicine II, Fukushima Medical University School of Medicine, Fukushima, 960-1295, Japan
SO Annals of the Rheumatic Diseases (2001), 60(7), 685-689
CODEN: ARDIAO; ISSN: 0003-4967
PB BMJ Publishing Group
DT Journal
LA English
AB To examine the effect of transfection of oligodeoxynucleotides (ODNs) containing a CpG motif (CpG-ODN), of which the sequence was derived from circulating DNA in the sera of patients with systemic lupus erythematosus (SLE), on the expression of intercellular adhesion mol.-1 (ICAM-1) and synthesis of mRNA for proinflammatory cytokines and ICAM-1 in human umbilical vein endothelial cells (EC). A CpG-ODN or a control analog, GpC-ODN, was transfected into EC. ICAM-1 expression was examined by flow cytometry, and expression of mRNA in EC encoding interleukin 1 (IL1), IL6, IL8, tumor necrosis factor α (TNFα), interferon γ (IFNγ), and ICAM-1 was examined by semiquant. reverse transcriptase-polymerase chain reaction. The **CpG**-ODN augmented the expression of ICAM-1 on EC determined by flow cytometry and increased mRNA

levels of IL6, IL8, TNF.**alpha**., **IFN**γ, and ICAM-1, but the GpC-ODN did not. Synthesized DNA, with a sequence corresponding to that of the fragment containing the CpG motif, in sera of patients with SLE was found to enhance ICAM-1 expression on EC, suggesting the participation of circulating DNA fragments in the pathogenesis of vasculitis in SLE.

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 40 MEDLINE on STN DUPLICATE 12
AN 2002169644 MEDLINE
DN PubMed ID: 11902329
TI Importance of **CpG** dinucleotides in activation of natural **IFN-alpha**-producing cells by a lupus-related oligodeoxynucleotide.
AU Magnusson M; Magnusson S; Vallin H; Ronnblom L; Alm G V
CS Department of Veterinary Microbiology, Swedish University of Agricultural Sciences, Uppsala.. Mattias.Magnusson@vmm.slu.se
SO Scandinavian journal of immunology, (2001 Dec) 54 (6) 543-50. Journal code: 0323767. ISSN: 0300-9475.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200204
ED Entered STN: 20020321
Last Updated on STN: 20020611
Entered Medline: 20020411
AB The oligodeoxyribonucleotide (ODN) 5'-TTTTCAATTCGAAGATGAAT-3' (ODN H), identified in systemic lupus erythematosus (SLE) serum, induced the production of interferon (IFN)-alpha in human peripheral blood mononuclear cells (PBMC) when combined with lipofectin. Flow cytometric analysis with staining for surface antigens and intracellular IFN-alpha, showed that the IFN-alpha-producing cells (IPC) were the natural IPC, also termed type 2 dendritic cell precursors (pDC2) or plasmacytoid monocytes. The importance of unmethylated CpG dinucleotides for the interferogenic activity of ODN was studied. Methylation of CpG impaired the activity of single-stranded (ss) ODN H, but increased that of the complementary ssODN I. Furthermore, CpG-methylated double-stranded (ds) ODN Hmet-Imet lost, but hemimethylated dsODN H-Imet retained interferogenic activity. Inversion of the CpG to GpC had no effect on the interferogenic activity of ssODN H, increased that of ssODN I, however abolished the activity of dsODN H-I. Alteration of the CpG in ODN H to ApG and in the ODN I to CpT destroyed their activity. The induction of **IFN-alpha** is therefore sequence-specific, but unmethylated **CpGs** are not always required, especially not in ssODNs. Interferogenic DNA sequences could therefore be more frequent in eukaryotic genomes than previously thought and their capacity to activate natural IPC may have implications for immune responses to microbial antigens and nuclear autoantigens.

L12 ANSWER 17 OF 40 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:210659 BIOSIS
DN PREV200100210659
TI **Interferon-alpha**/-beta-mediated activation of human gammadelta T cells and NK cells by **CpG** oligonucleotides.
AU Rothenfusser, S. [Reprint author]; Hornung, V. [Reprint author]; Krug, A. [Reprint author]; Krieg, A. M.; Endres, S. [Reprint author]; Hartmann, G. [Reprint author]
CS Division of Clinical Pharmacology, Department of Internal Medicine, Ludwig-Maximilians-University, Munich, Germany
SO Immunobiology, (November, 2000) Vol. 203, No. 1-2, pp. 448. print.

Meeting Info.: Joint Annual Meeting of the German and Dutch Societies of Immunology. Duseldorf, Germany. November 29-December 02, 2000.
CODEN: IMMND4. ISSN: 0171-2985.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 May 2001
Last Updated on STN: 18 Feb 2002

L12 ANSWER 19 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:146704 CAPLUS
DN 132:278161
TI CpG-oligodeoxynucleotides enhance T-cell receptor-triggered interferon-γ production and up-regulation of CD69 via induction of antigen-presenting cell-derived interferon type I and interleukin-12
AU Kranzer, K.; Bauer, M.; Lipford, G. B.; Heeg, K.; Wagner, H.; Lang, R.
CS Institute of Medical Microbiology Immunology and Hygiene, Technical University of Munich, Marburg, 81675, Germany
SO Immunology (2000), 99(2), 170-178
CODEN: IMMUAM; ISSN: 0019-2805
PB Blackwell Science Ltd.
DT Journal
LA English
AB Bacterial cytidine-phosphate-guanosine (CpG-DNA) activates antigen-presenting cells (APC) and drives T helper 1 (Th1)-polarized immune responses in the mouse. Claims have been made that CpG-DNA costimulates murine T cells. The authors examined the direct and indirect effects of CpG-oligodeoxynucleotides (CpG-ODN) on human T-cell activation. CpG-ODN failed to costimulate purified human T cells activated with α-CD3 or α-T-cell receptor (TCR)αβ antibodies. In contrast, CpG-ODN sequence-specifically caused increased expression of CD69 on CD4 and CD8 T cells when peripheral blood mononuclear cells (PBMC) were stimulated via α-CD3. CpG-ODN and α-CD3 stimulation synergized to induce interferon-γ (IFN-γ) in T cells and natural killer (NK) cells, as shown by intracellular fluorescence-activated cell sorter (FACS) staining. These effects of CpG-ODN on human T cells were caused by the release of IFN type I (IFN-I) and interleukin-12 (IL-12) from PBMC. Enhancement of CD69 expression on α-CD3-triggered T cells could be reproduced in a coculture Transwell system of purified T cells and PBMC, was inhibited by neutralizing antibodies to IFN-I and could be mimicked by adding exogenous IFN-I. Furthermore, neutralization of either IFN-I or IL-12 diminished, and in combination abolished, IFN-γ production These findings show that CpG-ODN potentiate TCR-triggered activation of human T cells in an APC-dependent manner.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 20 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:124485 CAPLUS
DN 133:118560
TI Role of type I interferons in T cell activation induced by CpG DNA
AU Sun, S.; Sprent, J.
CS R.W. Johnson Pharmaceutical Research Institute, San Diego, CA, 92121, USA
SO Current Topics in Microbiology and Immunology (2000), 247(Immunobiology of Bacterial CpG-DNA), 107-117
CODEN: CTMIA3; ISSN: 0070-217X
PB Springer-Verlag
DT Journal; General Review
LA English
AB A review with 26 refs. on T cell activation in vivo following infection of

CpG DNA, roles of antigen-presenting cells and interferon type I in the activation of T cells by CpG DNA, and the adjuvant effects of interferon type I.

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 15

AN 2000195069 EMBASE

TI Stimulation of thymocyte proliferation by phosphorothioate DNA oligonucleotides.

AU Mannon R.B.; Nataraj C.; Pisetsky D.S.

CS R.B. Mannon, Nephrology Section, VA Medical Center, Building 6, 508 Fulton Street, Durham, NC 27705, United States. roslyn.mannon@duke.edu

SO Cellular Immunology, (10 Apr 2000) 201/1 (14-21).
Refs: 28
ISSN: 0008-8749 CODEN: CLIMB8

CY United States

DT Journal; Article

FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB DNA is a complex macromolecule the immunological properties of which depend on short sequence motifs called **CpG** motifs or immunostimulatory sequences (ISS). These sequences are mitogenic for B cells and can stimulate macrophage cytokine production. While these sequences do not directly activate T cells, they can augment effects of stimulation via the TCR. Furthermore, ISS can affect T cells because of macrophage production of IL-12 and **IFN**-.**alpha**./β.
In these studies, we further evaluated the immune effects of DNA on T cells, testing the possibility that certain T cell populations can respond directly to this stimulus. We therefore tested the in vitro responses of thymocytes to a series of phosphodiester (Po) and phosphorothioate (Ps) oligonucleotides (ODNs) varying in sequence. In in vitro cultures, phosphorothioate ODNs (sODNs) containing **CpG** motifs induced significant proliferation of murine thymocytes, although phosphodiester compounds lacked activity. The magnitude of stimulation varied with sequences flanking the **CpG** motifs, as both dA and dT sequences enhanced the stimulatory capacity of the **CpG** motif. Furthermore, **CpG** sODNs were strong costimulators of anti-CD3- mediated thymocyte activation, increasing proliferation compared to anti-CD3 in the absence of DNA. This activation was only partially inhibited by cyclosporine A and was not dependent on a calcium influx. Together, these results indicate that phosphorothioate oligonucleotides containing **CpG** motifs can directly induce thymocyte proliferation as well as augment TCR activation. These observations thus extend the range of actions of **CpG** DNA and suggest additional mechanisms for its function as an immunomodulatory agent or adjuvant. (C) 2000 Academic Press.

L12 ANSWER 24 OF 40 MEDLINE on STN DUPLICATE 16

AN 2000040430 MEDLINE

DN PubMed ID: 10570325

TI Anti-double-stranded DNA antibodies and immunostimulatory plasmid DNA in combination mimic the endogenous IFN-alpha inducer in systemic lupus erythematosus.

AU Vallin H; Perers A; Alm G V; Ronnblom L

CS Section of Immunology, Department of Veterinary Microbiology, Swedish University of Agricultural Sciences, Uppsala, Sweden.

SO Journal of immunology (Baltimore, Md. : 1950), (1999 Dec 1) 163 (11) 6306-13.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991220
AB Patients with systemic lupus erythematosus (SLE) have increased blood levels of IFN-alpha, which correlate to disease activity. We previously identified an IFN-alpha-inducing factor (IIF) in the blood of SLE patients that activated the natural IFN-alpha-producing cells in cultures of normal PBMC. The SLE-IIF contained DNA and IgG, possibly as small immune complexes. In our study, we demonstrated that SLE-IIF correlated to the presence of anti-dsDNA Abs in patients and contained anti-dsDNA Abs as an essential component. Purified anti-DNA Abs or SLE-IgG caused only a weak IFN-alpha production in cultures of normal PBMC in the presence of costimulatory IFN-alpha2b. However, they converted the plasmid pcDNA3, which itself induced no IFN-alpha production in PBMC, into an efficient IFN-alpha inducer. A human monoclonal anti-ss/dsDNA Ab had the same effect. This **IFN-alpha**-inducing activity of the plasmid was abolished by methylation, suggesting that unmethylated **CpG** DNA motifs were important. Like IIF in SLE serum, the combination of SLE-IgG and pcDNA3 appeared to stimulate IFN-alpha production in natural IFN-alpha-producing cells, a unique cell population resembling immature dendritic cells. The IFN-alpha production was greatly enhanced by IFN-alpha2b and IFN-beta, and for SLE-IIF it was also enhanced by GM-CSF but inhibited by IL-10. We have therefore identified a new function of DNA-anti-DNA Ab complexes, IFN-alpha induction, that might be important in the pathogenesis of SLE.

L12 ANSWER 28 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 19
AN 1999308565 EMBASE
TI How BCG led to the discovery of immunostimulatory DNA.
AU Tokunaga T.; Yamamoto T.; Yamamoto S.
CS T. Tokunaga, Fukuoka Jo-Gakuin University, 3-42-1 Osa, Minami-ku, Fukuoka 811-1313, Japan. tokunaga@fukujo.ac.jp
SO Japanese Journal of Infectious Diseases, (1999) 52/1 (1-11).
Refs: 91
ISSN: 1344-6304 CODEN: JJIDFE
CY Japan
DT Journal; General Review
FS 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The concept of immunostimulatory DNA was borne in a long series of studies on BCG-mediated tumor resistance. DNA purified from BCG inhibited the growth of various syngeneic animal tumors, augmented NK cell activity and induced **IFN-.alpha./**β and -γ from mouse spleen cells and human PBL. Extending the lines of study, we found two biologically remarkable facts that (i) DNAs from invertebrates, but not from vertebrates and plants, showed the above mentioned biologic

activities, and (ii) the activities were completely dependent on particular base sequences having **CpG** motifs but in a senseless manner. Details of those early studies carried out mainly in the 1980's have been reviewed in the first part of this paper. In the middle part of this review the results of toxicity and pharmacology studies and clinical trials of BCG-DNA, performed by other groups in Japan in the late 1980's, were introduced. Since a large amount of DNA had never been administered repeatedly into experimental animals or human, those experiences obtained seem to be worthwhile to introduce. Research interests of immunostimulatory DNA were galvanized in 1995 by the report of Krieg et al. showing murine B cell activation with bacterial DNA containing **CpG** motifs. Within a short period of time, a huge number of papers have been published in this field, and the study has expanded rapidly and largely. Now, it includes a number of research fields, for example, host-defense mechanisms against infection, allergy, autoimmune diseases, cytokine networks, plasmid vaccination, and therapeutic application of certain diseases. This paper reviewed briefly recent advances of immunostimulatory DNA research. The response of higher animals against immunostimulatory DNA must be the most primitive but important mechanism for self-nonself discrimination against foreign DNA. By utilizing immunostimulatory DNA or controlling this primitive response, it seems possible to offer many beneficial means to human health. For instance, more potent peptide- or plasmid- vaccines could be developed by the use of immunostimulatory DNA. On the other hand, many study results suggest that immunostimulatory DNA works either beneficially or harmfully for the hosts. We assume that further extensive and careful studies are required.

L12 ANSWER 30 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:11302 CAPLUS
DN 130:181339
TI Type I interferon-mediated stimulation of T cells by CpG DNA
AU Sun, Siquan; Zhang, Xiaohong; Tough, David F.; Sprent, Jonathan
CS The R. W. Johnson Pharmaceutical Research Institute, San Diego, CA, 92121, USA
SO Journal of Experimental Medicine (1998), 188(12), 2335-2342
CODEN: JEMEAV; ISSN: 0022-1007
PB Rockefeller University Press
DT Journal
LA English
AB Immunostimulatory DNA and oligodeoxynucleotides containing unmethylated CpG motifs (CpG DNA) are strongly stimulatory for B cells and antigen-presenting cells (APCs). We report here that, as manifested by CD69 and B7-2 upregulation, CpG DNA also induces partial activation of T cells, including naive-phenotype T cells, both in vivo and in vitro. Under in vitro conditions, CpG DNA caused activation of T cells in spleen cell suspensions but failed to stimulate highly purified T cells unless these cells were supplemented with APCs. Three lines of evidence suggested that APC-dependent stimulation of T cells by CpG DNA was mediated by type I interferons (IFN-I). First, T cell activation by CpG DNA was undetectable in IFN-IR-/- mice. Second, in contrast to normal T cells, the failure of purified IFN-IR-/- T cells to respond to CpG DNA could not be overcome by adding normal IFN-IR+ APCs. Third, IFN-I (but not IFN-γ) caused the same pattern of partial T cell activation as CpG DNA. Significantly, T cell activation by IFN-I was APC independent. Thus, CpG DNA appeared to stimulate T cells by inducing APCs to synthesize IFN-I, which then acted directly on T cells via IFN-IR. Functional studies suggested that activation of T cells by IFN-I was inhibitory. Thus, exposing normal (but not IFN-IR-/-) T cells to CpG DNA in vivo led to reduced T proliferative responses after TCR ligation in vitro.
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 32 OF 40 MEDLINE on STN DUPLICATE 21
AN 1998000985 MEDLINE
DN PubMed ID: 9341778
TI CpG-containing synthetic oligonucleotides promote B and cytotoxic T cell responses to protein antigen: a new class of vaccine adjuvants.
AU Lipford G B; Bauer M; Blank C; Reiter R; Wagner H; Heeg K
CS Institute for Medical Microbiology, Immunology and Hygiene, Technical University of Munich, Germany.. tb101bl@sunmail.lrz-muenchen.de
SO European journal of immunology, (1997 Sep) 27 (9) 2340-4.
Journal code: 1273201. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971114
AB Foreign DNA has been shown to impinge on immune cell function by an as yet unidentified mechanism. We and others have demonstrated that single-stranded (ss) DNA containing the motif **CpG** flanked by two 5' purines and two 3' pyrimidines are mitogenic for B cells and activate macrophages to release tumor necrosis factor-**alpha**, **interferon**-gamma, interleukin (IL)-6 or IL-12. Because of these pro-inflammatory responses we investigated if ssDNA would serve as a potential vaccine adjuvant. Here we show that CpG-containing oligonucleotides represent a powerful adjuvant for both humoral and cellular immune responses. When ssDNA was incorporated into inocula, specific antibody titers of the IgG2 isotype were enhanced by greater than 100-fold. Primary cytotoxic T lymphocyte responses generated to either unprocessed protein antigen or major histocompatibility complex class I-restricted peptide were exceedingly strong. Evidence is also provided that oligomers directly influenced T cell receptor-triggered T cell proliferation. Thus ssDNA oligomers may serve as inexpensive and safe vaccine adjuvants and, in addition, differential effects due to sequence may allow for directed responses.

L12 ANSWER 33 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 22
AN 1996:518346 CAPLUS
DN 125:165670
TI Induction of NK activity in murine and human cells by CpG motifs in oligodeoxynucleotides and bacterial DNA
AU Ballas, Zuhair K.; Rasmussen, Wendy L.; Krieg, Arthur M.
CS Department Internal Medicine, University Iowa College Medicine, Iowa City, IA, 52242, USA
SO Journal of Immunology (1996), 157(5), 1840-1845
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB We have recently show that oligodeoxynucleotides (ODN) containing unmethylated CpG dinucleotides (CpG motif) can induce B cells to proliferate, differentiate, and secrete cytokines. In this study we demonstrate that CpG motifs contained in ODN as short as 15 bases in length were quite effective at inducing NK cell lytic activity in vitro in both human and murine lymphocytes. Such ODN were also effective at inducing NK lytic activity, in vivo, in mice. Expts. designed to determine the cellular and cytokine requirements for NK cell induction revealed that B and T cells are not necessary, that the ODN do not augment the activity of highly

purified NK cells, and that the ODN augment NK cell activity indirectly by inducing the secretion of IL-12, IFN-αβ, and TNF-α.
Various ODN sequences were prepared to determine the optimal ODN length, motif, palindrome, backbone modification, and dose requirements. We found no requirement for a palindromic sequence but a definite requirement for an unmethylated CpG motif. While necessary, however, a CpG motif was not sufficient for NK cell induction. Instead, there appeared to be stringent requirements for the immediate flanking bases at the 5' and 3' ends as well as for flanking sequences outside the immediate 5' and 3' bases. In particular poly(G) ends seemed to exert seemed to exert a complex qual. and quant. effect which could be up- or down-modulating depending on whether the ODN backbone was phosphorothioate modified or not.

L12 ANSWER 34 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 23
AN 96228244 EMBASE
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TI Immunostimulatory DNA sequences necessary for effective intradermal gene immunization.
AU Sato Y.; Roman M.; Tighe H.; Lee D.; Corr M.; Nguyen M.-D.; Silverman G.J.; Lotz M.; Carson D.A.; Raz E.
CS Department of Medicine, S./R. Stein Inst. for Res. on Aging, University of California, 9500 Gilman Drive,San Diego, CA 92093-0663, United States
SO Science, (1996) 273/5273 (352-354).
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LA English
SL English
AB Vaccination with naked DNA elicits cellular and humoral immune responses that have a T helper cell type 1 bias. However, plasmid vectors expressing large amounts of gene product do not necessarily induce immune responses to the encoded antigens. Instead, the immunogenicity of plasmid DNA (pDNA) requires short immunostimulatory DNA sequences (ISS) that contain a **CpG** dinucleotide in a particular base context. Human monocytes transfected with pDNA or double-stranded oligonucleotides containing the ISS, but not those transfected with ISS-deficient pDNA or oligonucleotides, transcribed large amounts of **interferon**-**alpha**., **interferon**-β, and interleukin-12. Although ISS are necessary for gene vaccination, they down-regulate gene expression and thus may interfere with gene replacement therapy by inducing proinflammatory cytokines.

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